BASIC SCIENCE **TEMEL BİLGİ**

NEUROSONOLOGY OF EMBOLI DETECTION AND MONITORING

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ABSTRACT

Cerebral embolism is the leading cause of ischemic stroke. Detection of microembolic signals [MES] in cerebral circulation is uniquely attained by several transcranial Doppler techniques, and can not be obtained with any other available imaging modality. Albeit no uniform picture has emerged from the studies, presence and amount of MES can identify a high-risk status in the setting of potential arterial or cardiac sources of cerebral embolism. Real-time MES monitoring during vascular procedures with high cerebral embolism risk seems also promising. The potential of MES detection in improvement of patient care is usually acknowledged, even though several aspects remain yet to be scientifically established. We herein review theory, technique and clinical potential of the neurosonological emboli detection, and try to add to understanding of the journal readership about the recent development on this subject.
Key Words: Transcranial Doppler, microembolic signal, patent foramen ovale, M-mode, multi-gate, robotic ambulatory monitoring.

EMBOLİ SAPTAMA VE MONİTORİZASYONUNUN NÖROSONOLOJİSİ

ÖZET

Serebral embolizm iskemik inmenin en sık nedenidir. Dolaşımda mikroembolik sinyal (MES) saptanması transkranial Doppler (TCD) dışında hiçbir mevcut teknik ile ulaşılamayan ve gelecek inme riskini ortaya koymada kritik önemi olduğu hemen her çalışmada saptanmış olan bir yöntemdir. Gerçek zamanlı MES varlığı semptom durumuna bakılmaksızın yüksek risk statusunu işaret eder. MES bulunuşuna göre tedavi adaptasyonunun hasta özelinde yararlı olduğu konusu henüz karara bağlanmamış olmakla birlikte potansiyelin yüksek olduğu genellikle düşünülmektedir. Bu derlemede nörosonolojik emboli belirleme ve sayımının teorisi, tekniği ve klinik potansiyeli detaylı olarak ele alınmaktadır.
Anahtar Sözcükler: Transkranial Doppler, mikroembolik sinyal, patent foramen ovale, M-mod, multi-gate, robotik ambulatuar monitorizasyon.

The fact that emboli can cause ischemic stroke is known since the 17th century. It is now evident that embolism is the most frequent cause of cerebral infarction. Sources of embolism can be located in the heart or in the parent arteries including arcus aorta, the carotid and vertebral arteries and other cerebro-petal arteries. In addition, cerebral embolism can originate from a peripheral venous source passing through a right to left shunt in the cardiac or pulmonary circulations such as patent foramen ovale and pulmonary arteriovenous malformations (paradoxical embolism). Except for their occasional visualization in the retinal circulation, routine diagnosis of embolic stroke can be considered as a "guilt by association". In other words, diagnosis of embolic stroke is established upon detection of occlusion in a previously normal artery in the presence of an appropriate embolic source in a patient with stroke. Detection of an embolic source might require an extensive work-up including transthoracic and transesophageal echocardiography, electrocardiography and Holter monitoring, carotid and transcranial Doppler ultrasonography, computerized tomography angiography, magnetic resonance angiography or even conventional angiography. This approach is similar to searching for the murder weapon in a

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crime scene. Although finding the weapon in the correct setting is very important, it only suggests the presence of an association and can not be considered as a direct prof. The association can be further strengthened by demonstrating the bullets in the body, and nowadays, several magnetic resonance imaging characteristics provide such information in at least a non negligible portion of the cases. However, a more definite link between the murder weapon and the crime can be established by the ballistic work-up, the detection of emboli by transcranial Doppler ultrasonography (TCD). The additive value of emboli detection and monitoring by TCD in the diagnosis of embolic stroke is one of the main subjects aimed in this review.

In the late sixties, intravascular gaseous microembolism was demonstrated by Doppler in the vena cava and aorta of sheep and swines following decompression after exposure to hyperbaric air. In 1972, decompression related peripheral vein and pulmonary artery gaseous emboli were shown in human experimental divers (1). This was followed by detection of arterial aeroembolism in the common carotid artery during cardiopulmonary by-pass. In 1980, a spectrogram display of an aeromicroemboli was obtained by Merril Spencer for the first time. Five years after introduction of Doppler insonation of intracranial arteries with 2 MHz probes by Rune Aaslid in 1982, gaseous microembolism during coronary by-pass was shown in the middle cerebral arteries (MCA) by Padayachee (2). In 1990, Merril Spencer reported a similar but lower intensity signals in the MCA during manipulation of the carotid arteries before arteriotomy during carotid endarterectomy (3). This was the first demonstration of nongaseous microembolic signals in a vessel. After Spencer's publication, a skepticism appeared in germane literature that these signals were anything other than artifacts or simply flow turbulence, but subsequent observations have clearly indicated that these Doppler signals were coming from thrombotic and/or atheromatous emboli.

Theory and measurement

Ultrasound is reflected when it is directed to an interface whose size is higher than the wavelength of the beam. This kind of interface is called as "specular reflector", and the amount of reflected sound depends on the acoustic impedance change from one media to another [Figure 1a]. Acoustic impedance (z), a measure of resistance to sound passing through a medium, is a product of density (ρ) times velocity (c) [z=ρxc] and is expressed as kg/m2/sec or "Rayl". One "Rayl" is equal to 10-6 kg/m2/sec. High-density materials have high velocities, and therefore have high acoustic impedances. Similarly, low-density materials, such as gases, have low acoustic impedances. If the acoustic impedance of an embolus is different from that of the blood stream, more sound will be reflected at the interface compared to transmitted. The reflection coefficient (αR) is multiplied by 100, and gives the percentage of reflection [αR = [(Z2-Z1)/(Z2+Z1)]2. As seen, it does not matter which impedance is higher or lower for the two materials making the specular interface because the difference between the two impedances gives the same number when the square is obtained. If the acoustic impedance difference is small, the intensity of the reflected sound wave is small, or vice versa. The acoustic impedances of blood and air are 1.6x106 kg/m2/sec and 0.0004x106 kg/m2/sec, respectively, and percent reflection at the blood air interface is (% reflection= [(Z2-Z1) / (Z2+Z1)]2 = [(1.6x106 – 0.0004x106 / 1.6x106 + 0.0004x106]2x100 = 99.9% (4).

When the interface size is smaller than the wavelength of the incident ultrasound beam, "nonspecular reflection", also called as "Rayleigh scattering" occurs instead of specular reflection. Lord Rayleigh found that the intensity of scattering was proportional to "d6xf4 " (5). In this case, each interface point acts as a new separate sound source, and reflects the sound to all possible directions [Figure 1b]. In the blood, the main reflectors are red blood cells (RBCs) and their size ranges from 7 to 10 μm. The wavelength of the ultrasound wave produced by 2 MHz transducers is 0.77 mm [Wavelength (λ)=c/f=Velocity/frequency] and for 10 MHz transducers λ=0,15 mm. One can think at the first glance that increasing the transducers frequency would facilitate detection of emboli since the emboli may then behave as specular rather than nonspecular reflectors. However, this will not be possible because of shallower penetrance of the beam. Specular reflection will determine the intensity of ultrasound returning to the transducer rather than scattering. Gases cause a large reflection of

ultrasound, and therefore gaseous microembolic signals are easy to determine. Understandably, gaseous emboli are the first reported kind of embolic materials by Doppler.

The audio signal, sometimes inappropriately called as "time domain signal", resembles an amplitude modulated sine wave (Figure 1b). An embolus travelling at a single velocity produces a brief pure-tone audio signal. This corresponds, according to the Fourier's theory, to a localized range of frequencies in the sonogram (5). This is one of the signal characteristics of microembolic signal, and named as "frequency centering". Frequency centering makes microembolic signals (MES) visible on the sonogram. The intensity of a MES depends on the shape, size and composition of the embolus, its trajectory and the level of insonation by the beam. In addition to these parameters, the velocity of a MES also depends significantly on the Doppler angle. Because both speed and trajectory of a MES change during their travel in a sample volume, the Doppler angle is impossible to estimate. Tissue-level disturbance of Doppler sample volume shape and unpredictable geometric relationship between the sample volume and the artery also contribute (6). These all result in a significant variation of the measured frequency of MES (5). This feature is named as "frequency modulation". As mentioned later in the article, frequency modulation is one of the characteristics of aeroembolism.

It is important to state that currently available commercial MES detection methods are usually based on the appraisal of the "measured embolus-to-blood ratio" (MEBR) not specular reflection. Normally, ultrasound scattered from erythrocytes produces varying regions of high and low intensity in the sonogram called as speckles. Motion of an embolus through the sample volume generates a very short duration increase in the intensity of backscattered ultrasound, which makes brighter signal compared to the surrounding speckle in the sonogram (figure 1c).

MEBR is measured in several different ways. In frequency domain analyses, the peak or mean value (decibel) for MES, and mean or median value for the background in a predefined time frame (window) and frequency range can be used. At this point, it should be noted that how and where the average scattering from blood is sampled is critical, because some algorithms use a more focal measurement window such as a similar location where the embolus passed in the preceding or following cardiac cycle while others use longer time frames. Albeit the measurement area is usually confined to the spectrogram, some algorithms can also use entire sweep screen including empty areas as well, where the frequency

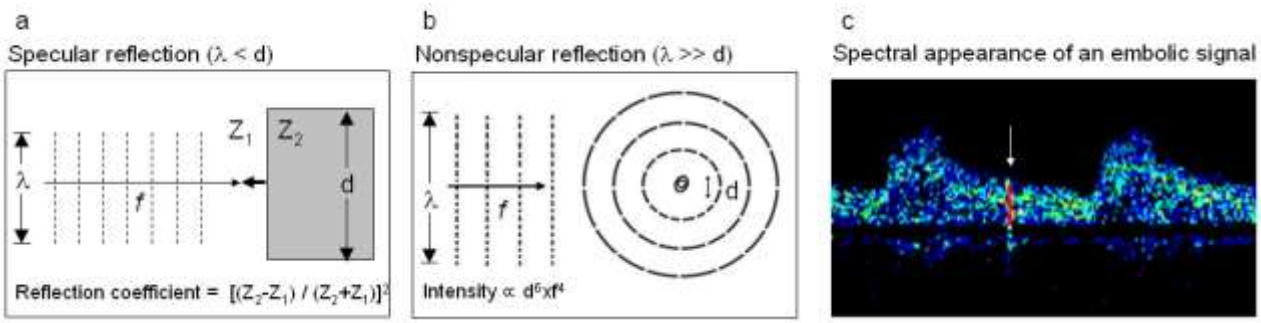

Figure 1: If microembolus size is small in relation to the wavelength of incident ultrasound, the sound wave will not be reflected (a: specular reflection) but scattered in almost every direction (b: Nonspecular reflection of Rayleigh scattering). MES are hyperintensity transients in conventional Doppler spectrograms (c, white arrow).

scale and its main determiner pulse repetition frequency (PRF) become significant.

The detection threshold is one of the principal MEBR features for automated algorithms used in MES determination. A range from 3 to 9 decibel is usually recommended as the lower limit enabling discrimination of MES from general background noise transients and spontaneous speckles. It is important to note that it has not been studied in detail whether the threshold decibel defined for MCA is also applicable to the other cerebral arteries or to stenotic or post-stenotic flow sonograms with spectral broadening. Individual calibration during emboli-free periods

is suggested for these cases (7).

Gain setting, sample volume and transducer frequency are also key determinants of MEBR. MEBR is inversely related to the gain, probe frequency and the sample volume size (8). The other instrumental parameters affecting MES detection are the fast Fourier transform (FFT) resolution and temporal overlap, sweep rate, the dynamic range, filter settings and recording time (7). The TCD sample volume is a tear-drop like space. Its cross sectional diameter is determined by the beam-width, and can be accepted as uniform in the setting of fixed depth and transducer. The axial diameter of the sample volume can be changed by the sonographer. Because sample volume size has a definite effect on the MEBR, a MES detected in a large sample volume looks less intense than a similar one displayed in a smaller sample volume; a standardized sample size between 3 to 10 mm is suggested to get a repeatable detection. For MES detection, 2 MHz pulse ultrasound is routinely used and recommended (7). The sensitivity of higher frequencies such as 4-5 MHz is lower (9).

A FFT overlap should be at least 50% in emboli detection in order to prevent missing the spectral appearance of MES that might occur during the gaps of the frequency analysis (7). If a lower overlap such as 10% is used, the MES is still audible but there will be no spectral signature of this signal (10). Because increase of sweep rate results in greater overlap (7), it would be wise to get short sweep time in patients with low number of MES (8). The connection between temporal and frequency resolution is mutual, and therefore if temporal resolution is needed to be increased, the frequency resolution automatically decreases. Because MES duration is less than 100 milliseconds by definition according to Frankfurt criteria (7), lower frequency resolution for emboli detection in the range between 64 to 128 Hz should be used. Newer frequency estimation techniques such as the Wigner transform do not have the same limitation, and can be used for high resolution spectral emboli images (11).

The dynamic range is the range of echoes processed and displayed by the ultrasound system, from strongest to weakest. Because MES have significantly high intensity, high dynamic range is preferred (7). Usually, a 60 dB dynamic range is suggested to prevent amplitude aliasing. If the amplitude of an embolic signal exceeds the dynamic range, many extra spectral frequencies (mirroring) will be generated erroneously (8). In practice, minimizing the background signal by applying lowest possible power and gain is usually used to bring the strong embolic signal into the dynamic range.

The filter settings of the operating system are also important in MES detection. A fixed high- and low-pass filter is advised. High-pass filter suppresses low frequencies originating from arterial wall oscillations, known as clutter filtering, and usually is set to 100 Hz.

According to the Frankfurt criteria (7), one hour monitoring time is optimal for internal carotid artery (ICA) stenosis and atrial fibrillation. In the same set of criteria, 30-minutes recording time is suggested for subjects with prosthetic heart valve. However, later observations indicated that longer monitoring duration directly corresponds to better sensitivity without significant safety problem. It should be noted that emboli do not occur at regular intervals, but rather in clusters, and emboli monitoring can be finalized after several MES are already detected when their number is not a concern. If many MES are detected, the recording can be finalized at the fifteenth minute. When no emboli appear, the longest time suggested is 90 minutes for routine clinical settings (4). The embolic rate for a given artery is sometimes presented as number of emboli per hour.

As summarized above, many technical parameters of the ultrasound instrumentations can significantly affect the detectability of MES. Therefore, It is recommended to use constant settings and strictly conform to the Frankfurt consensus criteria (7) especially when this technique is being used in follow up studies.

Artifact rejection and emboli typing

There are two main areas of interest in emboli neurosonology. The first is automated discrimination of real embolic signals from and artifacts, known as “artifact rejection”. The second is determination of size and composition of an embolus.

In the Ninth International Cerebral Hemodynamics Symposium some minimum criteria for identification of MES were accepted (12). The advantage of the “1995 criteria” is their relative simplicity and ease for use. These include

very wide limits: for example, as seen in detail below, signals as long as 300 msec with intensity ratio of only 3 dB are accepted as MES. This simplicity is not only their power but also their weakness. Three years later, the International Consensus Group on Microembolus Detection published the consensus criteria following its Frankfurt meeting. The latter criteria set are cited as "Frankfurt criteria" in this text (7).

Artifacts, such as patient movement, talking, snoring, or probe manipulation, can also generate high intensity transient signals. Consequently, these signals could be identified as MES, if the software algorithm is not sophisticate enough. Table 1 summarizes the main differences between emboli and artifacts.

First of all, true embolic signals produce musical sounds, harmonic chirps, whistles, moaning or clicks, depending on their velocity. The reason of the chirping quality is not well understood. Frequency modulation is proposed as the cause (4), but not shown convincingly. If a microembolus passes at high velocities, it produces clicking or snapping sounds. However, the sound is like as moaning for slowly moving embolus. In contrast, for artifacts, or noise transient, the sound is not tonal or musical.

Table 1: Discriminative characteristics of HITS

HITS type	**MES**	**Artifact**
Duration (Millisecond)	Less than 100-300 milliseconds	Variable
Relative intensity increase	At least 3 dB	Variable
Frequency centering (focusing)	Present	Absent (Maximal at low frequencies)
Direction	Unidirectional	Bi-directional
Occurrence	Random [or quasi-random]** in the cardiac cycle	Everywhere, simultaneous with the occurrence of causes
Frequency modulation	Present	Absent
Sound	Characteristic, musical	Non-tonal, noise
Lambda (tail) sign	Present	Absent

Second, true embolic signals are very short transients. Their duration usually is less than 100 milliseconds (13) and by definition must be less than 300 msec (7). Their duration in the spectrum is inversely proportional to their velocity. The sample length of a MES is calculated as "velocity x time duration" and is usually greater than that represented by the device or calculated from the pulse duration. This apparent increase of sample length is not due to the differences of velocity differences between RBCs and the embolus. The reason is the greater scattering power of the embolus compared to that of the RBCs, making MES detectable on the borders of the sample volume where the echo from RBCs is too feeble to be detected at these regions (4).

Third, the amplitude of a real embolic signal exceeds that of the background signal by 3 decibels at minimum. Depending on the dynamic range, amplitude can be as high as 60 dB. Their intensity is generally frequency-focused, meaning that it is maximal over a narrow frequency range. Albeit remaining as a matter of debate, the amplitude of a MES may be related to composition and size of the embolus. However, energies of a noise transient are maximal in the low frequency range, and energies spread into higher frequency range when they are stronger. This feature usually allows easy differentiation of MES from artifacts.

However, inter-observer reliability is low among experienced observers when the intensity of MES is low, but it is excellent for high intensity signals.

Fourth, the real MES signal is unidirectional on the spectrogram while the noise transient are bidirectional as the frequencies spread away from the baseline. Sometimes, a mirror appearance with lower intensity at the other side of the zero line can accompany with real MES. This shadowing is called as lambda or tail sign, and is quite specific for MES (14-15).

Another feature of MES Doppler signature is their quite random occurrence in the cardiac cycle. This presumably is caused by random break-off from their source as well as their variable velocity, changing further in the flow streams as they travel, from their source to the point of recording. This feature is valid in cases of atrial fibrillation, monitoring during ICA stenting or endarterectomy but may not be seen in those with ICA stenosis. In the latter situation, MES generally aggregate at the pre-systolic period (16). However, the appearance of a MES is still random (the term of quasi-random may be preferred) in ICA stenosis because of the variable size and composition of particles coming from stenosis. In contrast, the instrumentation and patient related artifacts coincide with the cause,

and are not random (13).

Finally, real MES show frequency modulation, which is described as a change in MES frequency, and velocity as well, while passing the sample volume (5). The reason for the change in frequency is not totally clear. It may be due to wandering of the embolus from one flow stream to another during its transit in the sample volume due to a change in its velocity. However, it is demonstrated that almost all of the emboli stay at the same flow lamina during sample volume passage. As will be described in detail below, frequency modulation is more frequent in gaseous MES compared to particular ones.

Current MES detection technologies are time-consuming, expensive and labor intensive due to dependence of off-line auditory and visual analysis of every signal by expert observers. Therefore, practical and of course reliable automated embolus detection methods are needed for widespread acceptance of these techniques.

An automatic detection system should at least provide a sufficient reduction of the vast amount of data for the expert evaluation. A number of systems have already been developed based on various signal analysis techniques. Automated algorithms usually use two steps for embolic signal identification. The first step is determining of any signal with intensity exceeding the preset minimal threshold level (HITS step). The second is artifact rejection (MES step).

Comparison of the signal intensities above and below the zero line, determining the rapidity of increase of the signal intensity, recognizing of characteristic bell-shaped increase of MBER and use of neural network are used for artifact rejection (17). Among others, two of the commercially available methods of reliable artifact rejection that require mentioning are multi-gate recording and M-mode emboli tracking (Figure 2 a-c). In multi/dual-gate technology, discrimination between MES and artifacts can be achieved by

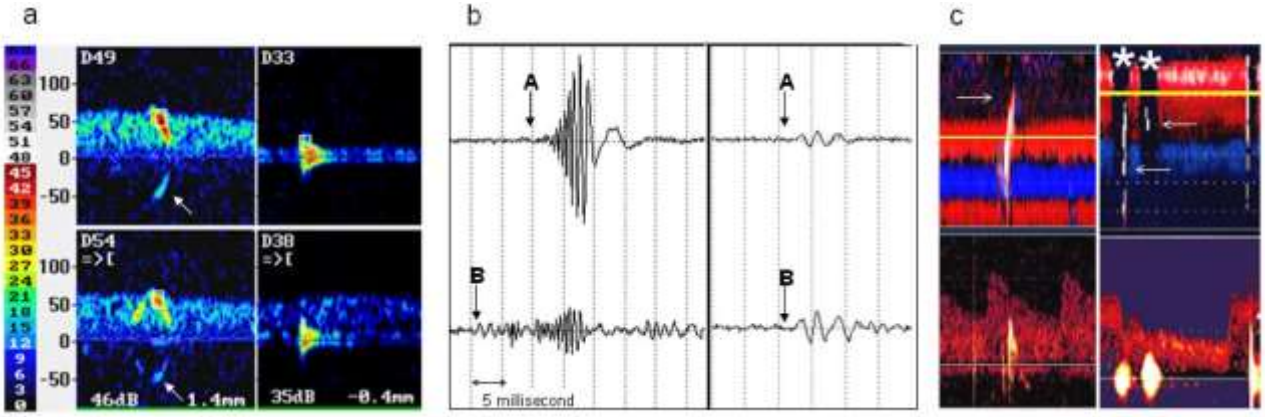

Figure 2: a: Spectrogram appearance of a MES and a cable movement artifact with dual-gate technology is displayed (on the left and right, respectively). MES signal shows lambda sign (white thin arrows), unidirectionality and frequency modulation while artifact is bidirectional. b: Analysis of raw Doppler provides more understanding about this technology. There is a time lag (A-B) of 8 miliseconds between the onset of the two raw signals denoting movement of the MES (on the left). Velocity of this MES was calculated as 41 cm/sec, which is almost equal to that provided by the system (45 cm/sec). In contrast, artifact signal appeared simultaneously in two depth (A-B=0). c: M-mode tracking demonstration of a MES shows characteristic bright tractus with a slope (open white arrow) indicating its movement distally.In contrast, an artifact caused by jaw clanching causes a straight tract with a signal void area typically surrounding it (white star).

simultaneous monitoring of multiple sample depths. Differentiation is based on the principle that MES appear sequentially in the insonated artery, while artifacts are observed at all depths simultaneously, regardless of the position of the insonation volume (18-19). Instead, high MEBR signal moving according to a predefined reference point can also be used for discrimination. In M-mode emboli tracking technology, MES are displayed as high-intensity sloped tracts. Detection of presence of this slope enables MES and artifact distinction because tracts of artifacts are vertical without slope. Darkened regions indicating signal void areas at the periphery of the tract are also specific for artifacts and can not be associated with MES on the M-mode display (20). It is important to

note that albeit several automated systems are currently being tested, no systems have been commonly acknowledged to be suitable for routine use. However, efforts to improve automated emboli detection should continue to increase not only extension of emboli detection duration, but also standardization. Determination of the composition and size of a microembolus is the second critical neurosonological issue in the area of emboli detection. First of all, it should be noted that exact determination of density and size of a MES cannot currently be attained from their MEBR values or any other sonogram characteristics (Figure 3) (21).

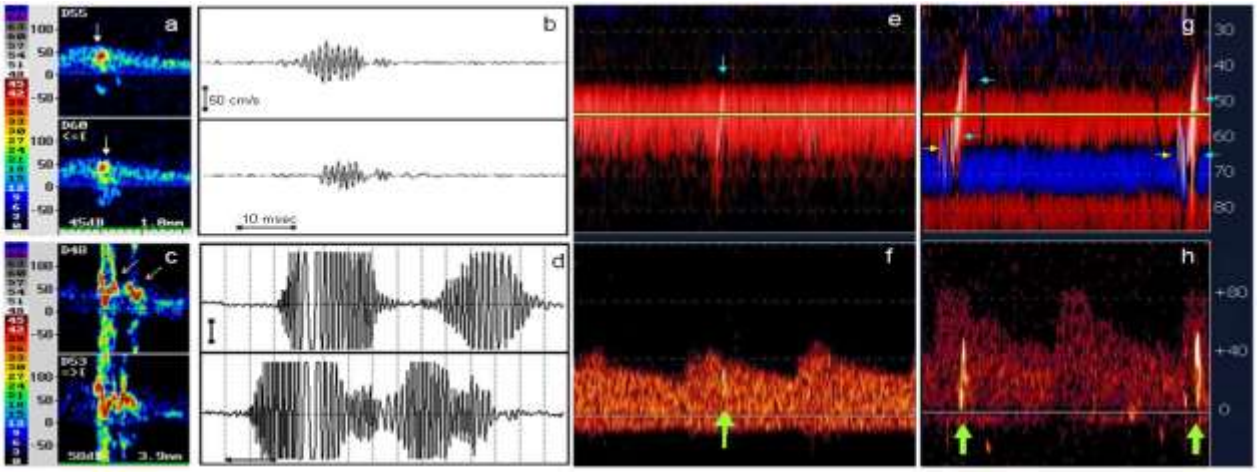

Figure 3: Typical sonogram (a) and time domain (b) appearance of a solid (formed, particulate) MES by dual gate technology. Signal duration and amplitude of this MES are lower than those of two gaseous (air) emboli documented on sonogram (c) and raw Doppler display (d). While a tail sign is associated with solid embolus, mirroring echoes are visible on the both side of the air emboli. Albeit frequency modulation is discernible for both type embolus, this is more exaggerated for aerogenic ones. A typical MCA solid MES signatures observed in a subject with critical ipsilateral ICA stenosis (where the MCA flow is significantly dampened) on M-mode (e, blue arrow) and corresponding single gate sonogram (f, yellow thick arrow). Two air emboli, seen on the M-mode display (g, blue arrow) and sonogram (h, thick green arrows), have brighter appearance compared to the solid ones. Of note, M-mode tracking indicates complex trajectory of MES in-transit: both are coming through TICA (blue track, blue arrows) and then entering into the MCA (red track, clue arrows) and later going distally.

For example, amplitude and duration are generally proportional to size, but not satisfactorily discriminatory. MEBR of aerogenic MES is higher than same sized solid MES because scattering of more ultrasound from gas bubbles, which are assumed as deformable spheres, compared to atheroma or thrombus of the same size particles, due to a greater difference in acoustic impedance (Table 2).

However, larger solid emboli can, at least theoretically, reach to same intensity and result in a considerable overlap. In other words, small gas bubbles and larger solid emboli produce similar signal characteristics. However, this problem can be overcome by using a statistical approach to estimate the proportion of solid and gas emboli as tested in conditions with large number of mixed embolic signals expected to occur such as coronary artery by-pass grafting (CABG). During CABG, population of solid

Table 2: Features can be used for discrimination of particulate and gaseous MES

MES type	**SOLID [Formed, Particulate]**	**GASEOUS [Aerogenic]**
Composition	Platelet aggregates, fibrin clots, atheromatous plaque materials	Gas, air, fat
Duration	Short	Long
MEBR	Low	High
Response to 100%O2	No	Significant decrease
Response to blood thinner	May present	Absent
Appearance in cardiac cycle	Quasi-random	Random
Flow modulation	Can be present	Absent
Frequency modulation	Usually absent	Present
Frequency response [Compressibility]	Absent	Present

*: Usually related to number of MES; **: Low quality, conflicted or non-replicated data.

microemboli originating from disturbed atheromatous plaques, which are generally quite small (in the 50-100 micron range), concentrate in the lower intensity band, while gaseous emboli originating from pump, whose MEBR values usually exceed 40 dB, concentrate at significantly higher intensity band. Because gaseous MES with MEBR lower than 10 dB (corresponding to small size less than 4 mm in diameter) tend to dissolve before reaching the cerebral circulation (22), this type of statistical approaches can be useful (16).

Perhaps the most dependable way of discrimination of MES are their response to medication or intervention. Lack of association with INR suggests that MES are gaseous rather than solid particulate during CABG. The same is also true for patients with prosthetic or artificial cardiac valves and decompression sickness. After giving a blood thinner such as intravenous heparin or dextran during CABG or carotid endarterectomy (CEA) the particulate MES will disappear, but no change in the number of gaseous MES is expected (23-24). In contrast, a substantial reduction of the MES count after inhalation of 100% oxygen (normobaric hyperoxia) indicates these MES are gaseous (25-26). Increase of inhaled oxygen fraction results in increase of the oxygen concentration in the blood and mutual decrease of nitrogen concentration. Because the solubility of oxygen in blood is almost 5 times higher than that of nitrogen, oxygen gas bubbles dissolve much easily and therefore have a shorter life span. As a result, fewer gaseous microemboli enter the cerebral circulation. Hyperbaric hyperoxia raising the concentration of dissolved oxygen about 10 times compared with normobaric conditions results in more effective cavitation and increases the rate of gaseous MES (27). Of course, both will have no effects on solid MES seen in these patients.

Frequency modulation is another characteristic of gaseous MES, and can be used for discrimination of gas and solid emboli. Due to erratic trajectories and tendency to be compressed by pressure from the ultrasound beam, change in shape, size, velocity and intensity of a gaseous MES is more common compared to solid emboli. While a solid embolus usually follows a fixed flow lamina to travel, a gaseous embolus usually wanders from one flow stream to another continuously. Absence of these changes makes frequency modulation negligible for particulate MES. A MES causing temporary disruption of blood flow in the MCA is called as flow-modulating emboli. These are relatively larger, and their MEBR are usually higher than 35 dB (5). Flow modulation MES is seen in less than 1% of patients during post-CEA period. Hypothetically, the diameter of a flow-modulating MES must be at least 2.5 mm to obstruct MCA lumen entirely to stop blood flow (16). It is important to note that small and flow-modulating emboli can be seen concurrently in a patient, and their number is not related each other. Accordingly, approximately 60% of solid emboli after CEA are less than 0.2 mm in diameter while only 2% of emboli are wider than 0.8 mm in diameter including several flow modulating ones (16). It is important to note that flow modulation can not be seen with gaseous MES and is confined only to particulate emboli.

Albeit all of the fore-mentioned features would be useful in differentiation of solid MES from gaseous ones, the real improvement was achieved after automated detection of frequency response of gaseous MES. Discrimination is particularly important because gaseous emboli are relatively harmless, but particulate ones are not. Because of their small size, gaseous microemboli easily pass through the capillary bed without blockage of microcirculation. The size of a particulate embolus producing a similar MEBR is much larger and can block capillary bed and eventually lead to ischemia.

Gaseous emboli are small bubbles. They become smaller and more rounded within the bloodstream. Smaller gas bubbles become better Rayleigh scatterers. By increasing the frequency of the ultrasound beam a little bit, for example from 2 to 2.5 MHz, the intensity of Rayleigh scattering is greatly increased because of the compressibility of gases. In other words, solid microemboli reflect more ultrasound at the higher than at the lower frequency (2.5 MHz > 2.0 MHz), whereas the opposite is correct for gaseous microemboli. This was proposed as an adjunct to distinguish solid emboli from gaseous ones (28).

In the study describing this technique (28-29), the multi-frequency TCD insonating simultaneously with 2.5 and 2.0 MHz, successful description rates were 95.6% for in vitro solid spheres and 94.3% for gaseous bubbles. In 15 patients with mechanical heart valves, of 433 MES identified, 84.2% was gaseous, 14.4% was solid and only 1.4% was uncertain of nature. In 38% of the 45 patients with carotid stenosis, of 32 MES

detected, 93.7% was classified as solid and 6.3% as uncertain. Also, the system correctly classified artifacts in 99.3% of the occurrences. After this system has become commercially available (EmboDop® by DWL), several studies tried to replicate these highly successful rates but were unsuccessful. In one study, 145 MES in 23 symptomatic carotid stenosis patients and 648 MES during 50 bubble studies were evaluated. The system was found to be neither sensitive for solid emboli (sensitivity: 50.3%, specificity: 94.2%) nor specific for gaseous bubbles (sensitivity: 95.6%, specificity: 50.3%) (30). In another study, of 1256 MES signal identified by an expert during 22 CABG operations in the left MCA, only 59.6% were correctly identified, and classified as solid or gaseous by the machine. In other words, 40.4% was missed by the system. Of note, the percentage of false-negative MES varied between 19.4% and 73.1% (mean 40%) individually (31). Indeed, as stated by its inventors (32), accuracy of multi-frequency TCD for emboli identification is not good enough when plenty of emboli appeared in the same sample volume simultaneously as occurring during bubble test in the setting of large right-to-left shunts.

Albeit one hour monitoring is currently considered as sufficient for non-operative conditions such as ICA stenosis, prolonged time of recording has a potential to increase MES detection rate (33-34). In addition to advent of new electronic and battery technology along with automated MES detection and typing software, Doppler signal loss problem due to disturbance of probe fixation frequently occurring during prolonged recording should be alleviated to attain this aim (35). Otherwise, enormous low-quality data requiring analysis will emerge from this kind of recording. A recently introduced robotic headband technology for auto-tracking and restoration of Doppler signal caused by probe detachment and patient movement is a forward step for prolonged time ambulatory MES detection in out-patient settings (36).

Clinical utility and relevance

Embolism is considered to be the most prevalent mechanism leading to brain infarction today. TCD allows noninvasive monitoring of in vivo embolism. Yield of emboli detection has extensively been studied in various clinical conditions (Table 3). It is important to note in advance that MES is not detectable in normal persons, and their occurrence indicates presence of an active source of embolism (37).

In any condition, presence of MES suggests high stroke risk regardless of the subjects' symptom status. In other words, when detected in an asymptomatic person, MES indicates high risk situation for stroke and mandates active search for the source. And, when detected in a subject after index event, they indicate again a high risk for recurrence. Presence of MES can also confirm the diagnosis of embolism when etiological classification of cerebral ischemia remains uncertain. Furthermore, in the patients with two or more potential sources of embolism such as those with concomitant ICA stenosis and atrial fibrillation, spatial distribution of MES may help in identification of the active lesion. In addition to their prognostic significance, MES presence and count can be used as a surrogate marker in clinical decision making in various conditions. The utility of emboli detection was extensively investigated in patients with ICA stenosis, early after acute stroke and peri-operative period of CEA (Table-3).

Although the clinical yield of MES detection has not been demonstrated convincingly enough in intracranial arterial stenosis, nonvalvular atrial fibrillation, cardiac valvular diseases including prosthetic heart valves, and other vascular procedures with high risk for cerebral embolism other than CEA, thepresence and high load of MES has almost invariably been connected to higher stroke occurrence of recurrence.

Cervical ICA stenosis

Presence of MES in a patient with ICA stenosis indicates unstability. First of all, MES are more frequent in recently symptomatic ICA stenosis (38). When compared to subjects with asymptomatic stenosis, not only MES prevalence but also their number is higher in symptomatic patients (39-40).

During one hour monitoring performed in the ipsilateral MCA, MES can be detectable in up to 50% percent of the symptomatic cases while they are present in only 10% to 17.5% of the asymptomatic ones (40). There is also an inverse relationship between the frequency of MES in the ipsilateral MCA and the interval passed since the

Table 3: Presence of MES and future cerebrovascular events

Predictive value of MES*	Disease	Procedural
Probable	Asymptomatic high-grade carotid stenosis Symptomatic carotid stenosis	Carotid endarterectomy Carotid stenting Coronary artery by-pass grafting Cerebral aneurysm embolization
Possible	Asymptomatic carotid stenosis MCA stenosis Acute stroke	Cerebral angiography Left ventricular assist device implantation
No value Unknown**	Prosthetic cardiac valves Non-valvular atrial fibrillation Carotid dissection After acute myocardial infarction Anti-phospholipid syndrome Aortic arch atheroma Endocarditis Patent foramen ovale Mitral valve prolapse Dilated cardiomyopathy Intra-cardiac thrombus	Monitoring of effectiveness of anti-platelet or anti-coagulant treatment Embolic source detection

*: Usually related to number of MES; **: Low quality, conflicted or non-replicated data.

last episode of ischemic cerebral symptoms. In other words, MES are found more frequently when tested soon after occurrence of symptoms (41). These observations suggest that carotid artery plaques only temporarily produce MES, and may coincide with their vulnerable characteristics. Secondly, MES prevalence is higher in patients with moderate (at least 50%) or more severe stenosis compared to mild ones (38, 42-43).

Thirdly, prevalence of MES may increase in cases with vulnerable, or malignant, atherosclerotic ICA plaques. Albeit not a uniform finding (39, 44-45), majority of studies indicated that several ultrasonic plaque characteristics such as ulceration (46), surface thrombosis (46) and irregularity (43), heterogeneous appearance (43) and echolucency or hypoechogenicity (47-48) are associated with increased MES prevalence.

In accordance with these observations, clinical studies showed that presence of MES independently predicts subsequent short-term stroke and/or TIA risk in patients with ICA stenosis regardless of symptom status (49). A recent meta-analysis documented a positive link between presence of MES and stroke or combined stroke and transient ischemic attack (TIA) risk for symptomatic carotid artery stenosis (270 patients, OR:9.57 [95% CI:1,6-59.3] and OR:6.36 [95%CI: 2.9-13.9], respectively) and for asymptomatic carotid artery stenosis (677 patients, OR:7.46 [95%CI: 2.24-24.9] and OR:12.0 [95%CI: 2.4-59.3], respectively), despite heterogeneity among studies (50). Another systematic review of 586 patients with symptomatic and 1066 patients with asymptomatic ICA stenosis showed comparable results, such that the presence of at least one MES, which was more prevalent in symptomatic patients (43% versus 10%), indicated an increased stroke risk in both symptomatic (OR: 7.7 [95%CI: 3.6-15.4]) and asymptomatic patients (OR: 13.4 [95%CI:6.5-24.7] 13.4) (51). In prospective ACES (The Asymptomatic Carotid Emboli Study) study performed in 467 patients with asymptomatic ICA stenosis, MES positivity was seen in 16.5% of the population. Yearly stroke occurrence was 3.62% in MES positive patients compared to 0.7% in MES negative ones, indicating significant increase in stroke risk (OR: 5.57 [95%CI: 1.6-19.3]). Combined risk of TIA and stroke risk was also increased in patients with MES (prevalence: 7.13% vs 3.04%, OR: 2.54 [95%CI: 1.2-5.4] in MES positive and negative patients, respectively) (52).

In patients with carotid artery disease, MES monitoring can also be utilized as a surrogate marker to evaluate the effectiveness of antiplatelet medication, as suggested by the CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis) trial (53). This trial has shown that a clopidogrel and aspirin combination is more effective than aspirin monotherapy at reducing asymptomatic embolism in patients with recently symptomatic carotid artery stenosis of at least 50%.

Acute stroke

The presence of MES was found to be predictive of both recurrence of stroke alone (OR=2.44 [95%CI: 1.2-5.1)] and recurrence of either stroke or TIA (OR=3.71 [95%CI: 1.6-8.4]) in acute stroke patients according to a meta-analysis performed in 737 patients (50). Albeit frequency of MES was 24% in average in this meta-analysis, heterogeneity among studies included is again significant. In patients with acute stroke, MES is typically found in arteries distal to active lesion. Studies have consistently shown that MES are

most frequently observed in patients with large artery disease, are less frequent in those with cardioembolic stroke, and are infrequent or absent in patients with lacunar stroke (54). Albeit these encouraging initial results, incorporation of MES monitoring into the acute stroke care is early, and requires further controlled studies.

Carotid endarterectomy

Microembolic signals are seen in almost every CEA operation. Intra-operative MES count is high during shunt insertion, dissection and clamp release. These MES can be either due to air or solid embolism. In contrast, MES occurring before arteriotomy and after artery closure are mostly particulate type and have greater clinical significance. MES load during these intervals are connected to new asymptomatic ischemic lesion on diffusion weighted imaging in several studies.

Available data indicate that occurrence of intra-operative stroke is related to emboli load, and MES count exceeding the 70-100 range increases this risk. Therefore, any decline in intra-operative MES number may be important. Several modifications of surgical techniques such as minimal manipulation prior to arteriotomy, early control of distal internal carotid artery lumen (55) and usage of dual antiplatelet therapy prior to surgery (56) can be useful for this purpose.

Persistence of microembolization after carotid flow restoration is a significant indicator of postoperative stroke risk. A recent meta-analysis, including 649 patients from 5 studies, confirmed the association between high frequency of MES immediately after CEA and risk of peri-operative stroke alone (OR=24.54 [95%CI: 7.8-76.4]) and stroke and TIA combined (OR=32.1 [95%CI: 11.4-90.4]) (50). After CEA operation, denuded area of endothelium released after atheroma removal is a potent stimulant for platelet adhesion and aggregation, and creates a source of embolism. The peri-operative stroke rate is between 2% and 8% after CEA. Approximately, a quarter of these strokes are related to operational hypoperfusion, and the remaining three-quarters are secondary to cerebral embolism. In patients with high grade ICA stenosis, MES number and frequency are expected to decrease significantly following CEA after a transient increase in the first hours of post-operative period. During this immediate period, high MES count was shown to be connected to development of new cerebral infarction. However, the cut off value for post-operative MES number varied from 10 (57) to 50 (58) per hour in different studies, and remained beyond consensus.

It is useful to note that excessive microembolisation should not be interpreted as a certain indication for re-exploration after CEA unless there is evidence for new symptoms and/or a significant fall of the ipsilateral MCA velocity. Medical management is suggested, at least initially, for these patients, and one of the frequent causes can be inadequacy of anti-platelet medication. For patients with ipsilateral abundant MES after CEA, testing and adjustment of anti-platelet efficacy (23), use of intravenous Dextran-40 (24, 59), low molecular weight heparin but not IV unfractioned heparin (60) and platelet GP IIb/IIIa receptor antagonist (61) are suggested as relevant options to decrease early stroke and TIA risk.

Current data suggest procedural microembolization to the brain may result not only in immediate clinically obvious cerebrovascular events but also long-term cognitive dysfunction. Given the absence of uniformly demonstrated cut off value for MES number for development of long-standing post-CEA neuropsychological deterioration, it is wise to prevent their occurrence as much as possible.

Final word

In addition to unavailability of user-friendly automated methods for detection and discrimination of MES, disturbingly low detection prevalence during short recording times (up to one hour), probably resulting from temporal variability in embolization rates, makes MES detection a low-yield test for risk stratification, especially in low-risk subgroups of asymptomatic ICA stenosis and atrial fibrillation, where the technology is greatly needed. This problem can be alleviated after advent of an ambulatory TCD system for long-term monitoring capability like a cardiac Holter monitor equipped with robotic signal adaptation, automatic emboli detection and typing (35, 62). Preliminary clinical results of a prototype of this kind of system are quite promising because a reasonable quality signal could be recorded for several hours. Although the potential for MES detection to improve clinical practice seems promising, it should be noted that the technology is still at its beginning, and the full extent will only become apparent over time. Requirement of further experimental and clinical

studies to improve our understanding of this subject is obvious.

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